IV. Remarks

Claims 1-22 are pending.

Claims 5, 9, 10, 14, and 17-22 stand rejected under 35 USC §112, 2nd ¶, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner contends that Applicants use of the term "between about ... and about" is indefinite. Further, the Examiner queries whether a value on the range could be less than zero. Applicants respectfully request reconsideration in light of this response.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The Federal Circuit has explained that the second paragraph of § 112 contains two requirements: "first, [the claim] must set forth what the applicant regards as his invention, and second, it must do so with sufficient particularity and distinctness, i.e., the claim must be sufficiently definite." ***Solomon v. Kimberly-Clark Corp.***, 216 F.3d 1372, 1377, 55 USPQ2d 1279, 1282 (Fed. Cir. 2000). In determining whether the claim is sufficiently definite, the Courts and PTO must analyze whether "one skilled in the art would understand the bounds of the claim when read in light of the specification." ***Personalized Media Communications, LLC v. Int'l Trade Comm'n***, 161 F.3d 696, 705, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998). In the present case, the Examiner contends that Applicants' Claims are not definite because the use of the word "about."

The Courts have long held that the term but the term "about" means approximately or nearly and is a clear warning that exactitude is not in the claim, but rather it contemplates variation. ***See Syntex (U.S.A.) Inc. v. Paragon Optical Inc., 7 USPQ2d 1001 (Dis. Az. 1987).*** Accordingly, the claim may be interpreted as: between approximately or nearly and is a clear warning that exactitude is not in the claim, but rather it contemplates variation. For example, in regards to Claim 9, the Claim language contemplates variation of a diameter of between about "5 cm and abut 2.0m"; for Claim 10, a variation of about "10cm and about 100cm"; for Claim 14, a variation of "about 1.0g ... and about 25.0g"; and for Claims 17; a variation of the pH; and, for Claim 21, a variation in the percentage hexanediol. Exactitude is not in the Claims. Therefore, there is no ambiguity in what the claim is claiming. The use of the word is an art accepted term. Application of the above tests illustrates that there is a definite definition where one skilled in the art would understand the bounds. Accordingly, Applicants respectfully request reconsideration.

Further, the Examiner's question of whether, for Claims 20 and 21, the amount of hexane could be less than 0% is easy to answer. One skilled in the art would know, without any question, that the amount of hexane claimed could not be less than 0%. Applicants respectfully request reconsideration of the rejection.

Claim 22 stands rejected because the Examiner states that it is not clear what "further purification" means. Applicants respond by pointing the Examiner to the specification, on page 12, line 31 to page 13, 11, without limitation. Here numerous examples and literature references

are given as to further purification and/or processing. Applicants respectfully request reconsideration of the rejection in light of this response.

Applicants extend their thanks to the Examiner for indicating allowable subject matter. Applicants will seek allowance of the remainder of the claims prior to rewriting the Claims indicated free of the prior art in independent form.

Claims 1-4, 6, 9, 10, and 22 stand rejected under 35 USC §103(a) as being unpatentable over US Pat. No. 6,008,041 (hereinafter referred to as the '041 patent) in view of US Pat. No. 5,801,039 (hereinafter referred to as the '039 patent) and in further view of the 1998 Varkey publication in the Journal of Peptide Research 51, 49-54 (hereinafter referred to as the Varkey article). Applicants respectfully request reconsideration in light of this response.

The Examiner contends that the '041 patent teaches a method for purifying human growth hormone by reverse phase liquid chromatography wherein the column has a diameter of 30 cm. The Examiner admits that the '041 patent does not disclose a method where the column is filled with a diol.

Next, the Examiner contends that the '039 patent teaches that adding a diol to an aqueous mixture stabilizes protein in the mixture.

Lastly, the Examiner contends that the Varkey article teaches that a 1,6 hexanediol resin in an aqueous mixture containing peptides that has good salvation properties.

The Examiner then concludes that given the advantages taught by the '039 patent of adding a diol to an aqueous mixture and that 1,6 hexanediol lends stability to a resin, as taught by

the Varkey article, it would have been obvious to one of ordinary skill in the art to use a 1,6 hexanediol to stabilize the aqueous solution in the '041 for purifying human growth hormone by reverse phase chromatography. Applicants request reconsideration in light of the teachings of the prior art sited by the Examiner and the lack of teaching and/or suggestion to make any combination.

To begin, the '039 patent is directed towards enzymes/proteases for detergents. The few lines identified by the Examiner are in reference to long term storage of the protease solution. See the '039 patent, Col. 13, ll. 46-49. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

Next, the Varkey article discloses synthesis of thioredoxin partial sequences on 1,6-hexanediol diacrylate-cross linked polystyrene resin. The process used a flexible polystyrene-hexanediol support (2% polystyrene cross-linked with 1,6-hexanediol diacrylic) to synthesize small peptide regions of Thioredoxin at small scale. This method was used to substitute for the Boc-benzyl ester strategy of Brany and Merrifield. Product removed from column with 33% MeOH in dichloromethane. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from thc column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

Lastly, the '041 patent provides the cDNA sequence encoding bovine dipeptidylaminopeptidase 1. Purified bovine dipeptidylaminopeptidase I was immobilized on a

CH Sepharose 4B support. This column was then used to further purify small amounts (5 mg) of Met-Asp Human Growth Hormone (met-asp HGH). The met-asp protein was further purified after ion exchange chromatography by a flow through method on the affinity column. This is affinity chromatography. No buffer system is mentioned. Further, having your product flowthrough the column does not demonstrate an operable column. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

The Examiner has not identified any suggestion linking these three pieces of prior art, to combine the abstract teachings. It is basic patent law that to establish a prima facie case of obviousness, an Examiner must, inter alia, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." ***In re Fine***, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved." ***Kotzab***, 217 F.3d at 1370, 55 USPQ2d at 1317.

However, as the Examiner has done here, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. ***See id.*** Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of

making the specific combination that was made by the applicant. ***See*** ***In re Dance*** , 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); ***In re Gordon*** , 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

Case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art refcrences. ***See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc.***, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing teaching or suggestion or motivation to combine as an essential evidentiary component of an obviousness holding); ***In re Rouffet*** , 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); ***In re Fritch***, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination only by showing some objective teaching leading to the combination); ***In re Fine***, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion essential to avoid hindsight); ***Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*** , 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it did not elucidate any factual tcachings, suggestions or incentives from this prior art that showed the propriety of combination). ***See also*** ***Graham***, 383 U.S. at 18, 148 USPQ at 467 (strict observance of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight.

See, e.g., Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this case, the Examiner fell into the hindsight trap. Here, there is no motivation, no suggestion, and hence, no obviousness.

Claims 1-4, 7, 11, 12, 13, and 16-19 stand rejected under 35 USC §103(a) as being unpatentable over US Pat. No. 5,994,511 (hereinafter referred to as the '511 patent) in view of the '039 patent and in further view of the Varkey article. Applicants respectfully request reconsideration ion light of the teachings of the prior art and the absence of any suggestion to combine the references.

In regards to the '511 patent, the disclosure at column 27,lines 20-21, is a standard list of chromatography resins that can be used as solid supports for the attachment of generic ligands. The purpose of the paragraph was just to mention that antibodies can be attached to solid supports by standard published methods/processes. There is no teaching or suggestion of purifying a molecule from a mixture.

The disclosure at column 28, lines 38-43, only point out a list of transmembrane proteins in which an antibody might reach (the human growth hormone being just one in the list).

The disclosure at column 52, lines 31-36, mentions the advantage of mechanically stable matrices (compared to less stable agarose supports). These comments are already common knowledge to purification scientists and are used to promote the sale of resins by the

respective vendors. There is no relevance to the specific purification of human growth hormone or reverse phase chromatography or diol like buffer systems.

The disclosure at column 52, lines 38-40, lists a number of generic chromatography procedures that can be used to purify antibodies (not human growth hormone). Reverse phase chromatography is only one of many methods that is listed. Any purification scientist could generate this list. There is not teaching or suggestion to use the chromatographic methods for purifying priteins.

None of the passages from the '511 patent cited by the Examiner teach or disclose a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

As previously stated, and restated for the convenience of the Examiner, the '039 patent is directed towards enzymes/proteases for detergents. The few lines identified by the Examiner are in reference to long term storage of the protease solution. See the '039 patent, Col. 13, ll. 46-49. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

Further, as previously stated and restated for the convenience of the Examiner, the Varkey article discloses synthesis of thioredoxin partial sequences on 1,6-hexanediol diacrylate-

cross linked polystyrene resin. The process used a flexible polystyrene-hexanediol support (2% polystyrene cross-linked with 1,6-hexanediol diacrylic) to synthesize small peptide regions of Thioredoxin at small scale. This method was used to substitute for the Boc-benzyl ester strategy of Brany and Merrifield. Product removed from column with 33% MeOH in dichloromethane. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

Accordingly, the combination of the three references is not Applicants' invention. Further, there is no suggestion or teaching present in the prior art references to make the combination. Applicants respectfully request reconsideration.

Claims 1-4 and 15 stand rejected under 35 USC §103(a) as being unpatentable over US Pat. No. 6,437,101 (hereinafter referred to as the '101 patent) in view of the '039 patent and in further view of the Varkey article. Applicants respectfully request reconsideration in light of the teaching of the prior art and the lack of any suggestion to make a modification.

To begin, the '101 patent has no relevance to the claims of the application in question. The patent is directed towards methods for the isolation of human growth hormone, growth hormone antagonist, or a homologue of either, from a biological source. The methods of the invention utilize multiphase extraction. The '101 patent, at the most relevancy to the claims of the instant invention, discloses a solution containing proteins, hardly Applicants' invention.

As previously stated, and restated for the convenience of the Examiner, the '039 patent is directed towards enzymes/proteases for detergents. The few lines identified by the Examiner are in reference to long term storage of the protease solution. See the '039 patent, Col. 13, ll. 46-49. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

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The combination is not Applicants' invention. Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. ***See Graham v. John Deere Co***, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). However, it is fundamental that the combination must be Applicants invention. Here, the combination is not Applicants' invention. Accordingly, Applicants respectfully request

reconsideration.

Claims 1 and 8 stand rejected under 35 USC §103(a) as being unpatentable over the '041 patent in view of the '039 patent and in further view of the Yu article, from the Journal of Chromotography A, 1996, 149-155 (hereinafter referred to as the Yu article). Applicants respectfully request reconsideration based on the teachings of the cited prior art and the lack of suggestion.

As previously stated, but restated for the Examiner's convenience, the '041 patent provides the cDNA sequence encoding bovine dipeptidylaminopeptidase 1. Purified bovine dipeptidylaminopeptidase I was immobilized on a CH Sepharose 4B support. This column was then used to further purify small amounts (5 mg) of Met-Asp Human Growth Hormone (met-asp HGH). The met-asp protein was further purified after ion exchange chromatography by a flow through method on the affinity column. This is affinity chromatography. No buffer system is mentioned. Further, having your product flowthrough the column does not demonstrate an operable column. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

Likewise, as previously stated, and restated for the convenience of the Examiner, the '039 patent is directed towards enzymes/proteases for detergents. The few lines identified by the Examiner are in reference to long term storage of the protease solution. See the '039 patent, Col. 13, ll. 46-49. There is no teaching or suggestion of a method for purifying a molecule

from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

Further, as previously stated and restated for the convenience of the Examiner, the Varkey article discloses synthesis of thioredoxin partial sequences on 1,6-hexanediol diacrylate-cross linked polystyrene resin. The process used a flexible polystyrene-hexanediol support (2% polystyrene cross-linked with 1,6-hexanediol diacrylic) to synthesize small peptide regions of Thioredoxin at small scale. This method was used to substitute for the Boc-benzyl ester strategy of Brany and Merrifield. Product removed from column with 33% McOH in dichloromethane. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

The Yu article teaches and discloses a C18 alkyl diol silica resin in precolumn to separate analytes from proteins and polar endogenous compounds at small scale. Such techniques allow resins to have a hydrophilic as well as hydrophobic regions on the solid support (this is similar to the Varkey article). Embodiments of Applicants' invention disclose a solid phase which is hydrophobic and the hydrophilic portion is the mobile phase. Accordingly, the Yu article does not teach Applicants' invention.

The combination of these four references is not Applicants' invention. Moreover, and assuming, the combination is not suggested. It is basic patent law that there must be a suggestion to combine prior art. Here, the Examiner has simply found words within prior art

and made a combination. This is not permissible. Accordingly, Applicants respectfully request reconsideration of the rejection, in light of this response and the teachings of the cited prior art.

Lastly, Claims 1, 2, 4, and 5 stand rejected under 35 USC §103(a) as being unpatentable over the '041 patent in view of the '039 patent and the Varkey article and in further view of US Pat. No. 5,693,769 (hereinafter referred to as the '769 patent).

As previously stated, but restated for the Examiner's convenience, the '041 patent provides the cDNA scquence encoding bovine dipeptidylaminopeptidase 1. Purified bovine dipeptidylaminopeptidase I was immobilized on a CH Sepharose 4B support. This column was then used to further purify small amounts (5 mg) of Met-Asp Human Growth Hormone (met-asp HGH). The met-asp protein was further purified after ion exchange chromatography by a flow through method on the affinity column. This is affinity chromatography. No buffer system is mentioned. Further, having your product flowthrough the column does not demonstrate an operable column. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

Likewise, as previously stated, and restated for the convenience of the Examiner, the '039 patent is directed towards enzymes/proteases for detergents. The few lines identified by the Examiner are in reference to long term storage of the protease solution. See the '039 patent, Col. 13, ll. 46-49. There is no teaching or suggestion of a method for purifying a molecule from a mixture comprising: loading the mixture onto ma reverse phase liquid chromotagraphy

column; and eluting the molecule from the column with a buffer containing a diol selected from group consisting of 1,5 pentanediol, 1,6 hexanediol, and 1,7 heptanediol.

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The '769 patent discloses a reverse phase protein purification of Boc-Leu-enkephalin, in small scale. The buffer system of the '769 patent is not described. Contrary to this, one embodiment of Applicants' invention is for purification of proteins (specifically human growth hormone like proteins) at large scale and with a diol buffer system. The use of reverse phase purification at small scale, as in the '769 patent, is routine in many laboratories and is also used in analytical separation of proteins when assaying for protein purity. The small scale purification methods usually use acetonitrile in the buffer rather than diols that protect the proteins. The '769 is a small scale operation and is not applicable to Applicants' invention.

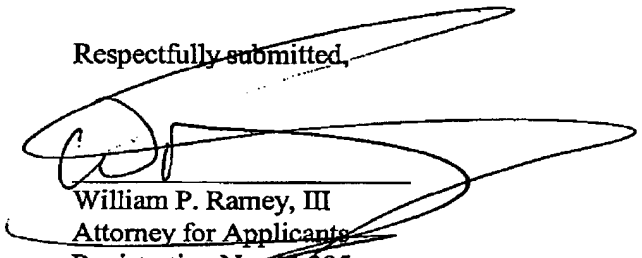
As can be seen, the combination of the four references is not Applicants' invention. Likewise, there is no suggestion to make any combination. Accordingly, the cited prior art is

not a valid obviousness rejection. Applicants respectfully request reconsideration, in light of this argument and the teachings of the prior art.

V. Conclusion

Applicants respectfully request reconsideration of the rejections and allowance of this Application. Should the Examiner feel an interview would further the prosecution of the case, Applicants invite the Examiner to contact the undersigned attorney. Please charge any required fees and credit any credits to deposit account number 02-2334. Further please charge the deposit account for a one month extension of time.

Respectfully submitted,



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